REMARKS

A. Objection to the Declaration

The Examiner objected to the declaration because it incorrectly claims to priority to Provisional Application No. 60/097,864, rather than Provisional Application No. 60/097,846. Applicant will submit a substitute declaration correcting this typographical error.

B. Rejection of Claim 2 Under 35 U.S.C. § 112, ¶ 2 for Indefiniteness

The Examiner rejected claim 2 as indefinite, asserting that the term "substantial muscle weakness" has not been defined, and that, thus, "said weakness might range from the undetectable to total paralysis." (Sec. 5(A) of Ofc. Act.) Applicant submits that the term "substantial muscle weakness" would be clearly understood by one of ordinary skill in the medical arts to refer to any muscle weakness within the range of that which is just clinically detectable using standard medical tests to total paralysis. Applicant thus respectfully traverses this rejection and requests that it be withdrawn.

C. Rejection of Claims 3, 5, and 6 Under 35 U.S.C. § 112, ¶ 2 for Indefiniteness

The Examiner rejected claims 3, 5, and 6 as indefinite, asserting that "'the' chemodenervating agent is properly 'said' chemodenervating agent." (Sec. 5(B).) Applicant submits that there is no statutory, regulatory, or case law basis for this rejection. The definite article "the" and the term "said" are believed to be well understood by parties involved in patent prosecution and claim interpretation, as well as by the public, to be interchangeable when used to refer back to an antecedent claim term introduced with the indefinite article

"a" or "an". Indeed, the Federal Circuit affirmed a U.S. District Court decision that held:

> [A] foundation or an antecedent basis must be laid for each element recited. This can be done[...]by introducing each element with the indefinite article ("a" or "an"). Subsequent mention of the element is to be modified by the definite article ["the"] or by "said" or by "the said," thereby making the latter mention(s) of the element unequivocally referable to its earlier recitation.

Slimfold Mfg. Co. v. Kinkead Properties, Inc., 626 F. Supp. 493, 496, 229 U.S.P.Q. 298, 299 (N.D. Ga. 1985) (quoting P. Rosenberg, 2 *Patent Law Fundamentals* § 14.06 (2d Ed.1984)), *aff'd*, 810 F.2d 1113, 1 U.S.P.Q. 2d 1563 (Fed. Cir. 1987). This decision states that the definite article (i.e. "the") *or* the term "said", or even the term "the said", may be used identically to "unequivocally refer[] to its earlier recitation" in the claim. *See also Wheeler v. Kleinschmidt*, 149 F.2d 161 (C.C.P.A. 1945); *Appl. of Ruskin*, 274 F.2d 955 (C.C.P.A. 1960); *Zenith Elec. Corp. v. Exzec, Inc.*, 1995 WL 275591, *5 (N.D. Ill. 1995); *Amsted Industr., Inc. v. ABC-NACO, Inc.*, 2001 WL 826904, *3 (N.D. Ill. 2001). Since the term "the chemodenervating agent" is used in claims 3, 5, and 6 to refer unequivocally to the antecedent recitation of "a chemodenervating agent", applicant respectfully traverses this rejection and requests that it be withdrawn.

D. Rejection of Claim 4 Under 35 U.S.C. § 112, ¶ 2 for Indefiniteness

The Examiner rejected claim 4 as indefinite, asserting that while the specification refers to "units", "mouse units", and "LD50 units", the term "'units' has not been defined." (Sec. 5(C).) These terms are used identically in

the specification to refer to units of a chemodenervating pharmaceutical measured using the mouse LD50 assay that is well-known by those of ordinary skill in the relevant art: "The botulinum unit is defined as that quantity of botulinum toxin capable of killing 50% of a population of Swiss Webster mice." (6th paragraph of "Background of Invention" section of specification.) With this assay, a single unit of chemodenervating pharmaceutical is defined as that amount which leads to the death of half the mice on average that have been treated with that amount. Applicant thus respectfully traverses this rejection and requests that it be withdrawn.

E. Rejection of Claim 6 Under 35 U.S.C. § 112, ¶ 2 for Indefiniteness

The Examiner rejected claim 6 as indefinite, asserting that "the term 'used' is vague and indefinite," and that "'other anti-inflammatory agents' is properly 'an other anti-inflammatory agent.'" (Sec. 5(D).) Applicant has amended claim 6 as suggested by the Examiner to replace "used" with "administered" and to replace "other inflammatory agents" with "an other inflammatory agent." Applicant notes that these amendments serve only to more clearly point out the invention, and do not in any way alter the scope of claim 6. Applicant submits that this amendment obviates the rejection of claim 6 and thus respectfully requests that the rejection be withdrawn.

F. Rejection of Claims 7 and 8 Under 35 U.S.C. § 112, ¶ 2 for Indefiniteness

The Examiner rejected claims 7 and 8 as indefinite, asserting that "'the' other agent is properly 'said' other agent." (Sec. 5(E).) Applicant submits that, for the reasons set forth in section (C) above, there is no basis in the patent

statutes, regulations, or case law that could justify this rejection. Since the term "the other agent" is used in claims 7 and 8 to refer unequivocally to the antecedent recitation of "an other inflammatory agent" in claim 6 as amended, applicant respectfully traverses this rejection and requests that it be withdrawn.

G. Rejection of Claim 12 Under 35 U.S.C. § 112, ¶ 2 for Indefiniteness

The Examiner rejected claim 12 as indefinite, asserting that "'the' hypersensitivity is properly 'said' hypersensitivity." (Sec. 5(F).) Applicant submits that, for the reasons set forth in section (C) above, there is no basis in the patent statutes, regulations, or case law that could justify this rejection. Since the term "the hypersensitivity" is used in claim 12 to refer unequivocally to the antecedent recitation of "Type I hypersensitivity" in claim 11, applicant respectfully traverses this rejection and requests that it be withdrawn.

H. Rejection of Claims 18 and 20 Under 35 U.S.C. § 112, ¶ 2 for Indefiniteness

The Examiner rejected claims 18 and 20 as indefinite, asserting that "'the' botulinum toxin is properly 'said' botulinum toxin." (Sec. 5(G).) Applicant submits that, for the reasons set forth in (C) above, there is no basis in the patent statutes, regulations, or case law that could justify this rejection. Since the term "the botulinum toxin" is used in claims 18 and 20 to refer unequivocally to the antecedent recitation of "*Clostridium botulinum* toxin" in claim 17, applicant respectfully traverses this rejection and requests that it be withdrawn.

I. Rejection of Claims 19 and 21-23 Under 35 U.S.C. § 112, ¶ 2 for Indefiniteness

The Examiner rejected claims 19 and 21-23 as indefinite, asserting that "'the' neurogenic inflammation is properly 'said' neurogenic inflammation." (Sec. 5(H).) Applicant submits that, for the reasons set forth in (C) above, there is no basis in the patent statutes, regulations, or case law that could justify this rejection. Since the term "the neurogenic inflammation" is used in claims 19 and 21-23 to refer unequivocally to the antecedent recitation of "neurogenic inflammation" in claim 17, applicant respectfully traverses this rejection and requests that it be withdrawn.

J. Rejection of Claims 17-23 Under 35 U.S.C. § 112, ¶ 1 for Lack of Written Description

The Examiner rejected newly-added claims 17-23 for lack of sufficient written description in the specification to reasonably convey to one of ordinary skill in the relevant art that the inventor had possession of the claimed invention at the time of filing.

With respect to claims 17, 19, and 21-23, the Examiner failed to find support in the specification for "a method for treating neurogenic inflammation" and "at least one neurogenic inflammatory mediator". (Sec. 7(A).) Applicant believes that support for these aspects of the invention are found amply throughout the specification. For example:

"[C]hemodenervative pharmaceuticals such as botulinum toxin...are effective anti-inflammatory agents." (Second paragraph of "Summary of Invention".)

"[A]nti-inflammatory action is explained by resultant blockage of mast cell and nerve cell release of histamine and other preformed mediators which result in vascular dialation, increased permeability, altered sensory experience, edema and erythema." (Third paragraph of "Summary of Invention".)

"The subject anti-inflammatory agent's unique property relates to the suppression of the component for the inflammatory response which occurs rapidly, and which is mediated by neural reflex mechanisms." (Sixth paragraph of "Summary of Invention".)

"[I]nflammation in torticollis in peripheral tissues may be neurogenically mediated." (Third paragraph of "Spasmodic Torticollis".)

Indeed, one of ordinary skill in the art, when reading the specification as a whole, would understand that the invention encompasses the treatment of neurogenic inflammation and the antagonism of at least one neurogenic mediator. All of the extensive discussion throughout the specification of mast cell and nerve cell release of "preformed mediators" and the blockage of such release by chemodenervating pharmaceuticals, such as botulinum toxin, would be clearly understood by one of ordinary skill in the art as referring to neurogenic inflammation and neurogenic mediators, and as indicating that the inventor had the invention as claimed in claims 17, 19, and 21-23 in his possession at the time of filing.

Regarding claim 19, the Examiner failed to find support in the specification for "substance-P, calcitonin gene-related peptide, vasoactive intestinal peptide, interleukin-1, interleukin-2, nitric oxide, 5-

hydroxytryptamine, tumor necrosis factor, and nerve growth factor. (Sec. 7(B).) In the first paragraph of the "Background of the Invention" section of the specification, applicant explicitly refers to inflammation as involving "complement, arachidonic acid metabolites such as prostaglandin and leukotrienes, cytokines, preformed mediators such as serotonin and histamine, and enzymes." One of ordinary skill in the art would understand that the term cytokine is defined in the art as referring to interleukin-1, interleukin-2, and tumor necrosis factor, and that 5-hydroxytryptamine is a synonym for serotonin. In the first paragraph of the "Summary of the Invention", applicant explicitly states that "low dosages of the subject chemodenervative agent reduces histamine release and releases of other preformed mediators associated with mast cell degranulation." In the second and third paragraphs of the "Mast Cells" section of the specification, applicant explicitly refers to "preformed mediators such as histamine, newly formed mediators such as leukotrienes and prostaglandins, cytokines, including interleukin-5, interleukin-8, kininogenase, and platelet activating factor", as well as "tumor necrosis factor alpha" and "substance P". Thus, support for the terms "substance P", "interleukins", "tumor necrosis factor", and "serotonin" are explicitly found in the specification. With regard to the other terms recited in claim 19, one of ordinary skill in the relevant art would clearly understand that applicant's explicit references in the specification to "preformed mediators", "cytokines", and "newly-formed mediators" encompasses all of the specific neurogenic inflammatory mediators enumerated in claim 19, and thus

indicates that applicant was in possession at the time of filing of the invention in every particular as claimed in claim 19.

For claim 20, the Examiner failed to find support in the specification for "wherein the botulinum toxin is less than about or equal to 1000 U". (Sec. 7(C).) Applicant has cancelled claim 20 without prejudice, thereby obviating this rejection.

For claim 22, the Examiner failed to find support in the specification for "wherein the neurogenic inflammation is caused by gout". (Sec. 7(D).) In the second paragraph of the section of the specification entitled "Rheumatoid Arthritis", applicant refers to the invention as offering "a means of localized application of an anti-inflammatory agent which is injected directly into joints...which creates an effect on the rapid inflammatory response and peripheral neural elements governing the inflammatory response." In other words, it is within the scope of the invention as disclosed in the specification to treat neurogenic inflammation of the joints. It is well understood by those of skill in the art that gout is a disease that is most fundamentally characterized by inflammatory response in the joints. Thus, one of ordinary skill in the relevant art would clearly conclude from applicant's statements in the specification regarding treatment of joint inflammation with chemodenervating pharmaceuticals that applicant was in possession at the time of filing of the invention as claimed in claim 22—including specifically the treatment of neurogenic inflammation caused by gout.

Regarding claim 23, the Examiner failed to find support in the specification for "treating the neurogenic inflammation by inhibiting histamine". (Sec. 7(E).) Applicant discloses in numerous places in the specification that it is within the scope of the invention to reduce inflammation by inhibiting histamine. For example, in the first paragraph of the "Summary of the Invention", applicant explicitly states that "low dosages of the subject chemodenervative agent *reduces histamine releases*" (emphasis added). Claim 15 as originally filed recites "botulinum toxin immunotypes which block mast cell release of histamine". Furthermore, in the various examples disclosed later in the specification, such as successful treatment with chemodenervative pharmaceuticals of cholinergic urticaria, treatment of blepharoconjunctivitis, etc., it is well known in the relevant art that those disorders are always associated with increased histamine activity in the affected tissues, and that increased histamine activity is a major cause of the inflammation. It would thus be clear to one of skill in the relevant art that applicant, at the time of filing, was in possession of the invention as claimed in claim 23—including the treatment of neurogenic inflammation by inhibiting histamine.

K. Rejection of Claims 2-5 Under 35 U.S.C. § 112, ¶ 1 for Lack of Enablement

The Examiner rejected claims 2-5 on the ground that the specification disclosure is insufficient to enable one of ordinary skill in the art to practice the invention as broadly as claimed without undue experimentation.

The Examiner failed to find support in the specification for a method for reducing inflammation without causing substantial muscle weakness and with

an effective dose of botulinum toxin of less than 2.5 units. The specification provides a number of working examples of treating inflammation with a chemodenervative pharmaceutical, such as botulinum toxin, without causing muscle weakness, and with doses within the claimed range. For example, in the fourth paragraph of the section of the specification entitled "Spasmodic Torticollis", applicant discloses a working example wherein "botulinum toxin injected into red areas noted to be painful and thermally active in accordance with the subject invention has been demonstrated to block the erythema, pain, increased tenderness, and heat loss within the area", and that "minimum doses [for achieving this effect] range between 0.6 units to 15 units and are *far lower than that required to produce regional weakness*" (emphasis added). As explained throughout the specification, and as well-understood by physicians for centuries, redness (erythema), pain, increased tenderness, and heat loss are some of the cardinal defining characteristics of inflammation. As another example, in the third paragraph of the section of the specification entitled "Conjunctivitis", applicant discloses as a working example "inject[ion] with .675 mouse units of botulinum toxin". Thus, one of ordinary skill in the art finds ample support in the specification for successfully treating inflammation with a chemodenervating agent, such as botulinum toxin, with a dose less than 2.5 units and without causing muscle weakness.

The Examiner also failed to find support in the specification for a method of reducing inflammation comprising administering botulinum toxins B-G. In the seventh paragraph of the "Background of the Invention", applicant

discloses that "botulinum is known to exist as immunotypes A-G", and that "each immunotype has been associated with varying durations of action and chemodenervating potency per LD 50 unit, as described by Borodic, G.E., Pearce, L.B., New Concepts in Botulinum toxin Therapy, Drug Safety 11(3): 145-152, 1994." The cited article describes the particular relative potencies per LD 50 unit of various immunotypes A-G of botulinum toxin. Thus, one of ordinary skill in the art could easily, and without undue experimentation, determine the appropriate dose of any of immunotypes B-G based upon the effective doses of immunotype A disclosed in the working examples of the specification. The potency relative to immunotype A could easily be determined by one of skill in the art simply by looking at the reference cited above, which was published well before the filing date of the present application. For example, the cited article clearly discloses that immunotype B exhibits a relative potency per LD 50 unit that is 1/50 to 1/100 that of immunotype A. Thus, one of ordinary skill in the art, without any undue experimentation , would be able to treat inflammation using a dose of botulinum toxin B in LD 50 units that is 50 to 100 times the dose disclosed in the specification as effective for botulinum toxin A. Furthermore, physicians skilled in the art titrate the dose upward from lower levels as individual variation in botulinum toxin dose response does occurs from patient to patient. This titration is not undue experimentation—rather, it is within the scope of ordinary medical practice in the use of pharmaceutical agents to treat human patients.

L. Rejection of Claims 1 and 5 under 35 U.S.C. § 102(e) as Anticipated by U.S. Patent No. 6,159,955

The Examiner characterizes the '944 patent as teaching "a method of reducing inflammation (anal fissures) comprising administering a botulinum toxin chemodenervating agent to an anatomic region (see particularly column 1, lines 25-33)." (Sec. 12.) The part of the specification cited by the Examiner is the only place where botulinum toxin is mentioned in the '944 patent, and reads as follows:

> Effective treatments for anal fissures, whether medical or surgical, involve relaxation of the spastic muscle. These treatments include lateral sphincterotomy, injection of the sphincter with botulinum toxin, and application of nitroglycerin ointment. A recent review by Sharp of treatment for chronic anal fissures recommends beginning with nitroglycerin ointment. If the fissure has not healed in six weeks, botulinum toxin injections are given.

The first sentence states that "effective treatments for anal fissures...involve relaxation of the spastic muscle." The second sentence states that "*these treatments* include...injection of the *sphincter* with botulinum toxin" (emphasis added). It is clear that the antecedent for "these treatments" is "effective treatments...involv[ing] relaxation of the spastic muscle", where the muscle is, of course, the sphincter muscle. Thus, botulinum toxin is being suggested as a treatment for anal fissures because of its ability to cause relaxation (i.e. weakening) of the sphincter muscle. There is no disclosure in the '944 patent that botulinum toxin could be used to reduce *inflammation* that might be associated with anal fissures—it is only disclosed as useful for causing muscle weakening.

Indeed, the only reference to inflammation in the context of anal fissures occurs in col. 5, lines 63-66 of the '944 patent. That section discloses that anal fissures cause pain as a result of a "combination of inflammation and spasm of the anal sphincter." This section thus specifically separates two distinct and independent causes for pain in anal fissures—inflammation and sphincter muscle spasm. In the section cited by the Examiner and quoted above, botulinum toxin is referred to solely as a method of relaxing sphincter muscle spasms, which have been explicitly distinguished from inflammation as independent causal agents in anal fissure pain. Botulinum toxin is disclosed in the '944 patent only as a means of reducing the sphincter muscle spasms involved in anal fissures, not for treating the distinct causal agent of inflammation. It is thus clear that the '944 patent does not disclose the use of botulinum toxin for treating inflammation. For this reason, applicant traverses this rejection, and respectfully requests that it be withdrawn.

M. Rejection of Claims 1, 5-6, and 17-23 under 35 U.S.C. § 102(e) as Anticipated by U.S. Patent No. 6,063,768

The Examiner has rejected claims 1, 5-6, and 17-23 as being anticipated by U.S. Patent No. 6,063,768. (Sec. 13.) Applicant notes that he filed a Request to Declare Interference with the '768 patent on May 14, 2001. Once these claims are determined to be otherwise allowable, the Examiner may determine if an interference should be declared with respect to these claims.

N. Rejection of Claims 1, 5-8, 10-12, and 17-23 under 35 U.S.C. § 103(a) over U.S. Patent No. 6,063,768 in View of the Merck Manual

The Examiner rejected claims 1, 5-8, 10-12, and 17-23 as *prima facie* obvious over the '768 patent and the Merck Manual. Applicant notes that he filed a Request to Declare Interference with the '768 patent on May 14, 2001. Once these claims are determined to be otherwise allowable, the Examiner may determine if an interference should be declared with respect to these claims.

In light of the foregoing, applicant submits that pending claims 2, 3, and 4 in this application are in condition for allowance, and a favorable action by the Examiner with respect to those claims is respectfully requested. Applicant further submits that claims 1, 5-8, 10-12, and 17-23 are in condition for allowance in every respect except with regard to the rejections over U.S. Patent No. 6,063,768. As explained above, applicant has filed a Request to Declare Interference between the present application and the '768 patent.

Applicant appreciates the Examiner's acknowledgement of the request for interference made in the Preliminary Amendment filed May 14, 2001. Examiner further points out in section 10 of the Non-Final Office Action mailed July 5, 2001, that no interference will be declared until "all pending claims are found allowable **and** Applicant has submitted appropriate evidence showing entitlement to said declaration" (emphasis in original). Applicant respectfully wishes to clarify that his understanding of the statutes, rules, and governing sections of the MPEP is that no interference shall be declared until all pending claims are found allowable *other than with regard to prior art rejections over the*

patent with which an interference is sought and applicant has submitted *prima facie* evidence of prior conception sufficient to show entitlement to a declaration of interference.

Applicant is greatly appreciative of the Examiner's prompt consideration of the claims, including those newly-presented in the Preliminary Amendment of May 14, 2001. Applicant reiterates his respectful request that examination of the instant application continue to be with "special dispatch" under 37 C.F.R. § 1.607(a)(6). Applicant intends to file *prima facie* evidence of entitlement to judgment under 37 C.F.R. § 1.608(b) as soon as is practicable, and respectfully requests that the examination of the instant application continue to proceed with special dispatch even in the interim.

If the Examiner is of the opinion that it would assist in placing claims 2, 3, and 4 in condition for allowance, and claims 1, 5-8, 10-12, and 17-23 in condition for allowance other than with regard to the prior art rejections over the '768 patent, or otherwise expedite prosecution, the applicant invites the Examiner to contact his counsel by telephone at the number listed below.

A one month extension of time is believed necessary for this filing, and is hereby petitioned for. The Commissioner is authorized to charge this extension of time or any other fees which may be required for this paper to Deposit Account Number 13-3250, Order No. 33677-00000.

Respectfully submitted,

Dated: November 5, 2001

By: _____

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